
The effect of antibiotic therapy for patients infected with *Helicobacter pylori* who have chronic urticaria

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Background: Several small trials looking at antibiotic therapy targeted at *Helicobacter pylori* for the treatment of chronic urticaria have been published and have had conflicting results. We conducted a systematic review of existing studies to help answer the clinical question of whether this therapy has a role in the treatment of chronic urticaria.

Methods: We identified studies published in the English language with searches of MEDLINE, PREMEDLINE, American College of Physicians Journal Club, Database of Abstracts of Reviews of Effectiveness, and Cochrane Libraries using the key words "*Helicobacter pylori*" and "urticaria." Relevant studies from bibliography reviews were also included. Studies included met the following criteria: (1) patients had urticaria for at least 6 weeks; (2) other known causes of urticaria were excluded by appropriate testing; (3) the initial diagnosis of *H pylori* infection was made by either serology, urea breath test, or upper endoscopy; and (4) an adequate trial of an antibiotic with known activity against *H pylori* was completed.

Results: In all, 10 studies met our inclusion criteria. The rate of remission of urticaria when *H pylori* was eradicated was 30.9% (59/191) compared with 21.7% (18/83) when *H pylori* was not eradicated; the background remission rate among control subjects without *H pylori* infection was 13.5% (10/74). When data from the 10 studies were combined, eradication of *H pylori* was both quantitatively and statistically associated with remission of urticaria (odds ratio 2.9; 95% confidence interval 1.4-6.8; $P = .005$).

Conclusion: We found that resolution of urticaria was more likely when antibiotic therapy was successful in eradication of *H pylori* infection than when patients who were infected did not achieve eradication. These results suggest that clinicians, after considering other causes of urticaria, should constitute (1) testing for *H pylori*; (2) treating with appropriate antibiotics if *H pylori* is present; and (3) confirming successful eradication of infection. (J Am Acad Dermatol 2003;49:861-4.)

Approximately 15% to 25% of the population will experience at least one episode of urticaria in their lifetime,¹ and an estimated one fourth of these people will have chronic urticaria.²

Chronic urticaria, defined as urticaria persisting for longer than 6 weeks, is, therefore, a common problem that frustrates patients and physicians alike. A variety of potential causes have been implicated, such as infections, food additives, medications, malignancy, physical factors, and vasculitis. A cause can be identified, however, in only the minority of cases of chronic urticaria.³

In the past several years, attention has turned to the microaerophilic gram-negative rod, *Helicobacter pylori*, as a potential cause of chronic urticaria.⁴ This potential link has enormous potential public health implications, as more than half of the world's population is thought to be infected with this organism.⁵

In addition to a well-accepted association between *H pylori* infection and peptic ulcer disease, gastric cancer, and low-grade lymphoma of gastric mucosa-associated lymphoid tissue, a host of ex-

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traintestinal maladies have been linked to the infection.⁶ Limited evidence is available, however, regarding an association between *H pylori* infection and dermatologic diseases such as urticaria, acne rosacea, atopic dermatitis, eczema, Schönlein-Henoch purpura, psoriasis, and systemic sclerosis. Such reports are largely on the basis of case reports or studies with small sample sizes and lack of appropriate control subjects. In addition, with respect to chronic urticaria, the available evidence on the efficacy of antibiotic therapy aimed at eradicating *H pylori* for the treatment of urticaria is conflicting.

Whether antibiotic therapy directed at *H pylori* is effective for the treatment of chronic urticaria (in patients with infection) is a potential subject for meta-analysis,⁷ but available reports are relatively few in number and differ in substantive ways. Accordingly, the goal of the current study was to conduct a systematic review of the efficacy of the antibiotic treatment of *H pylori* for patients with chronic idiopathic urticaria.

METHODS

Studies of the effects of *H pylori* eradication on the course of idiopathic chronic urticaria were retrieved from MEDLINE, PREMEDLINE, American College of Physicians Journal Club, Database of Abstracts of Reviews of Effectiveness, and Cochrane Libraries by using medical subject-heading and keyword searches for "*Helicobacter pylori*" and "urticaria." The search was conducted in April 2002, and included studies dating back to 1983, the year that *H pylori* was determined to be a pathogen responsible for gastrointestinal disease. We limited our search to those studies conducted in human beings and published in the English language. Bibliographies were also searched for relevant studies. Included studies met the following criteria: (1) patients had to experience urticaria for at least 6 weeks; (2) other known causes of urticaria were excluded by testing (eg, history, physical examination, complete blood cell count, erythrocyte sedimentation rate, C-reactive protein, thyroid-stimulating hormone, antimicrobial and antithyroglobulin antibodies, urinalysis, antinuclear antibody, protein electrophoresis, examination of stool for ova and parasites, antibodies to hepatitis B and hepatitis C, testing for physical urticaria, and serologic assessment for infection with *Streptococcus*, Epstein-Barr virus, and cytomegalovirus); (3) the initial diagnosis of *H pylori* infection was made by either serology, urea breath test, or by upper endoscopy; and (4) an acceptable trial of an antibiotic with known activity against *H pylori* was completed. Studies done in hospitalized inpatients, or in patients with gastrointestinal symptoms only,

were excluded to enhance the validity of our findings.

We only included studies in which there was an appropriate group for comparison; the effect of *H pylori* eradication with antibiotic treatment had to be compared with unsuccessful eradication with antibiotics, placebo therapy, or the spontaneous remission of patients with idiopathic chronic urticaria who were *H pylori*-negative. Urea breath testing and upper endoscopy results were used to determine whether eradication with antibiotic therapy was successful. If the information was not contained in the published report, personal communication was made with study authors to determine whether eradication therapy was successful. If follow-up evaluations were done on more than 1 occasion, the success rate at the last date of follow-up was used. In 1 published study,⁸ a double-blind, placebo-controlled, crossover design was used to evaluate the effect of treatment on 11 patients with *H pylori* infection. For purposes of our investigation, the 3 patients who were treated with placebo after unsuccessful antibiotic therapy and the 5 patients treated with antibiotics after placebo were assigned to separate treatment groups.

The data from each study were recorded in terms of the proportion of patients in remission among the group with eradication, compared with the proportion of patients in remission among the group without eradication (including patients who were *H pylori* positive treated with placebo). Two formal analyses were conducted: eradication versus unsuccessful eradication or placebo treatment, and eradication versus control subjects who were *H pylori* negative. Information on remission of urticaria among those who were *H pylori* negative was included for descriptive purposes. To account for the clustering of observations within each publication, a Mantel-Haenszel chi-square test (fixed-effects model) was used to calculate odds ratios, and corresponding *P* values and 95% confidence intervals.

RESULTS

Identification of studies

The search of MEDLINE and the Cochrane Libraries generated 25 articles when the medical subject heading key words "*Helicobacter pylori*" and "urticaria" were combined. Of these, we excluded 5 as single case reports; 2 for including patients with other known causes of urticaria; 1 for being a letter commenting on a published study; 4 for only determining causes of urticaria and/or immunologic associations and not providing information on outcomes of treatment; 1 for not having a control group or providing information on whether antibiotic ther-

Table I. Studies evaluating *Helicobacter pylori* and chronic urticaria

Study (reference)	No. of treated patients with urticaria and <i>H pylori</i> infection completing study	Reported age of patients with <i>H pylori</i> (y)	Follow-up evaluation (mo)	Eradication regimen*	Complete remission of urticaria when eradication of <i>H pylori</i> achieved	Complete remission of urticaria when eradication of <i>H pylori</i> not achieved	Remission of urticaria when patients with <i>H pylori</i> infection were treated with placebo or not treated with antibiotics	Remission of urticaria in patients without <i>H pylori</i> infection
Schnyder et al ⁸	11*	15–78	6	LA	1/3	2/7	1/9	
Erel et al ⁹	29	37.5 (median)	Not stated	OAC	1/25	0/4		
Wustlich et al ¹⁰	30	21–61 (mean 45)	6	OA	6/24	0/6		
Valsecchi and Pigatto ¹¹	31	24–61	8	OCM	3/29	0/2		1/25
Ozkaya-Bayazit et al ¹²	23	18–72 (mean 38.6)	6	OAC	4/17	2/6		3/8
Wedi et al ¹³	39	17–82 (mean 44.4)	6–9	OAC	14/21		5/18	6/14
Di Campli et al ¹⁴	18	46 (mean)	3	LAC	13/16	0/2		0/19
Tebbe et al ¹⁵	17	10–65	1.5–2.5	A or C or T and MBO	8/14	0/3		0/8
Dauden et al ¹⁶	15	22–67 (42.2 mean)	12	OAC	1/12	0/3		
Hook-Nikanne et al ¹⁷	53	14–70 (41.1 mean)	5	LM and A or T	8/30	3/5	5/18	
Totals	266				59/191	7/38	11/45	10/74

A, Amoxicillin; B, bismuth subsalicylate; C, clarithromycin; L, lansoprazole; M, metronidazole; O, omeprazole; T, tetracycline.

*Crossover design.

apy was successful in eradication of *H pylori*; 1 for treating only patients with gastrointestinal symptoms; 1 for not stating the duration of urticaria before enrollment; and 1 for only evaluating the effects of treatment in patients with infection and hereditary angioneurotic edema. Review of bibliographies yielded an additional report, yielding 10 studies for subsequent analysis.^{8–17} Among these 10 studies, 3^{13–15} claimed that antibiotic treatment for *H pylori* infection led to remission of urticaria in patients who were infected.

Age of study patients

The ages of the study patients varied greatly, with a range of 10 to 82 years (Table I). One study only reported the mean age,¹⁰ and another study⁹ only reported the median age.

Variability in antibiotic therapy

Antibiotic therapy varied among the different trials (Table I). Antibiotics were given from 7 days to 2 weeks, and proton pump inhibitors were administered concurrently for 7 days to 4 weeks.

Variability in time of follow-up evaluation

One study did not specify when the follow-up evaluation for determining resolution of urticaria occurred.⁹ The other trials evaluated patients 1.5 to 9 months after antibiotic therapy (Table I).

Remission of urticaria

The summary rate of remission of urticaria when *H pylori* was eradicated was 30.9% (59/191), compared with 21.7% (18/83) when *H pylori* was not eradicated. The background remission rate among control subjects who were *H pylori* negative was 13.5% (10/74) (Table I). When data from the 10 studies were combined, eradication of *H pylori* was both quantitatively and statistically associated with remission of urticaria, with an odds ratio of 2.9 (95% confidence interval 1.4–6.8; $P = .005$). Similar results were found (data not shown) in an analysis that excluded patients treated with placebo from the comparison group.

In a comparison of patients with *H pylori* eradication and control subjects who were *H pylori* negative, the odds ratio for remission of urticaria was 4.7 (95% confidence interval 2.6–17.6, $P < .001$).

DISCUSSION

Chronic urticaria is a common clinical disorder that may be extremely difficult to treat, with causes that often defy diagnosis. Infectious agents such as bacterial, viral, fungal, and protozoal organisms have been reported to be responsible for some of these cases.¹⁸ Whether *H pylori* has a role in the pathogenesis of chronic urticaria has engendered considerable debate. In addition, the results of treatment studies performed to date have been conflicting. Recommendations to initiate antibiotic treatment for *H pylori* infection for chronic urticaria should be evidence-driven, especially because eliminating *H pylori* would subject the patient to the cost of the antibiotics, a risk of antibiotic resistance development, medication side effects, and a potential increased risk of esophageal adenocarcinoma.¹⁹

We found that when antibiotic therapy was successful in eradication of *H pylori* infection, resolution of urticaria was more likely than when *H pylori* was not eradicated in patients with infection (or when successful eradication was compared with resolution in those not infected with *H pylori*). In this context, we believe that if patients infected with this organism are treated with antibiotics, clinicians should subsequently test patients with either breath testing or repeated endoscopy to ensure successful eradication.

It is important to note that even with successful eradication of infection with antibiotics, only one third of patients with *H pylori*-associated chronic urticaria were found to be in remission. Although *H pylori* apparently has a role in the origin of some cases of chronic urticaria, it appears that it may only be responsible for a minority of cases, even in patients who are infected. Because infection with *H pylori* is so common, many patients with chronic urticaria will have causes unrelated to *H pylori*, even in the presence of active infection.

The low eradication rate may also be explained in that some studies enrolled patients with positive serology for infection. Serology is inadequate to reveal the current activity of *H pylori* infection, however, and antibiotic treatment would not be expected to result in resolution of urticaria for patients without active infection.

Although our findings support the eradication of *H pylori* in patients with infection and urticaria, we acknowledge several shortfalls of our study. We were unable to conduct a formal meta-analysis, and cannot address issues related to publication bias, reports published in other languages, or heterogeneity of studies. In addition, we could be vulnerable to problems related to oversimplification of complex

issues.²⁰ We look forward to future studies to confirm or refute our findings.

Chronic urticaria is a considerable burden to patients and the health care system, and a cause is often not established, even after a thorough history, physical examination, and routine laboratory testing. Among such patients, testing for *H pylori* infection should be considered. If infection is documented, appropriate antibiotic-containing therapy and confirmation of eradication appear warranted.

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